UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/844,915 | 04/27/2001 | Paul David Robbins | AP32737-072396.0225 | 1483 |

21003 7590 09/03/2004

BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

| EXAMINER | |
|---|---|
| GIBBS, TERRA C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 09/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/844,915 | ROBBINS ET AL. | |
| | Examiner | Art Unit | |
| | Terra C. Gibbs | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 June 2004 and 01 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-7,9-15,17-30 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,7,10,11 and 30* is/are allowed.

6)☒ Claim(s) *4-6,12-15,17-29 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *March 1, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is a response to Applicants Remarks and Amendments filed March 1, 2004 and June 8, 2004.

Claims 3, 8, 16, 31, and 35-67 have been canceled. Claim 7 has been currently amended.

Claims 1, 2, 4-7, 9-15, 17-30, and 32-34 are pending in the instant application.

Claims 1, 2, 4-7, 9-15, 17-30, and 32-34 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Information Disclosure Statement*

Applicants Information Disclosure Statement filed March 1, 2004 is acknowleged. The references referred to therein have been considered on the Examiner.

### *Claim Rejections - 35 USC § 112*

In the previous Office Action mailed August 26, 2004, claims 10, 12, 15, 17, 18, 19, 20, and 26 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These rejections are withdrawn** in view of Applicants amendment to the claims to correct for insufficient antecedent basis.

In the previous Office Action mailed August 26, 2004, claims 7, 9, 11, 15, 17, and 19 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These rejections are withdrawn** in view of Applicants amendment to the claims to specify that the culturing step relates to the isolated dendritic cell of (b). The Examiner acknowledges that the claims have been amended to particularly point out and distinctly claim the tolerogenic dendritic cell in claims 9, 11, 12, 17, and 19.

In the previous Office Action mailed August 26, 2004, claims 1, 2, 4-7, 9-15, 17-30, and 32-34 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is withdrawn** in view of Applicants Amendment to the claims to recite wherein the oligodeoxyribonucleotide has the sequence set forth in SEQ ID NO:1.

In the previous Office Action mailed August 26, 2004, claims 1, 2, and 4-7, 9-14, 30, and 32-34, were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide, wherein the oligodeoxyribonucleotide is SEQ ID NO: 1, and further comprises an adenoviral vector encoding CTLA4Ig, and a method of making said isolated tolerogenic dendritic cell, does not reasonably provide enablement for an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, further comprising any viral

vector, and a method of making said isolated tolerogenic dendritic cell. **This rejection is withdrawn against claims 1, 2, 7, 10, 11, and 30** in view of Applicants amendments to the claims. **This rejection is maintained against claims 4-6, 12-14, and 32-34** for the reasons of record set forth in the previous Office Action mailed August 26, 2004.

***Response to Arguments***

In response to the rejection, Applicants argue that the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. Applicants argue that the specification clearly enables one of skill in the art to make and use the isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, wherein the NF-κB binding sites inhibit NF-κB transcriptional activity, wherein the oligodeoxyribonucleotide has the sequence set forth in SEQ ID NO:1, and further comprises a viral vector. Applicant relies on *In re Wands*.

Applicant's arguments have been fully considered, but are only found persuasive (*in part*). This rejection is withdrawn against claims 1, 2, 7, 10, 11, and 30 in view of Applicants amendments to the claims. Specifically, the amendment to the claims to specify that the oligodeoxyribonucleotide is SEQ ID NO:1 is found persuasive and therefore the 35 U.S.C. 112, first paragraph rejection against claims 1, 2, 7, 10, 11, and 30 is withdrawn. It is noted that claims 1, 2, 7, 10, 11, and 30 are drawn to an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, wherein oligodeoxyribonucleotide inhibits NF-κB transcriptional activity, wherein the oligodeoxyribonucleotide has the sequence set forth in SEQ ID NO:1, and do not further comprise a

viral vector. However, neither Applicants amendments, nor remarks have been found persuasive to overcome the 35 U.S.C. 112, first paragraph rejection against claims 4-6, 12-14, and 32-34. Applicants contend that the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. Applicants rely on *In re Wands*. However, the weighing of several factors as set forth in *Wands* was the standard applied under 35 USC 112, first paragraph rejection in the previous Official Action mailed August 26, 2004. Because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

The instant claims are drawn to an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, wherein the NF-κB binding sites inhibit NF-κB transcriptional activity, wherein the oligodeoxyribonucleotide has the sequence set forth in SEQ ID NO:1, and further comprises a viral vector, and a method of making said isolated tolerogenic dendritic cell. The specification as filed teaches an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, wherein the oligodeoxyribonucleotide inhibits NF-κB transcriptional activity, wherein the oligodeoxyribonucleotide has the sequence set forth in SEQ ID NO:1, and further comprises a viral vector encoding CTLA4Ig, and a method of making said isolated tolerogenic dendritic cell. The art teaches dendritic cells genetically engineered using adenoviral vectors are unpredictable. For example, Morelli et al. (Journal of Virology, 2000 Vol. 74:9617-9628) and Rea et al. (Journal of Virology, 1999 Vol. 73:10245-10253) teach dendritic cells genetically engineered using an adenoviral vector alone induces dendritic cell maturation (see Abstracts). However, Zhong et al.

(European Journal of Immunology, 1999 Vol. 29:964-972) and Tillman et al. (Journal of Immunology, 1999 Vol. 162:6378-6383) teach that dendritic cell maturation was not a function of recombinant adenoviral infection (see Abstracts). This contrast/contradiction in teachings is very critical since the instant application at page 5 [00010] teaches, "tolerogenicity may be enhanced in a host by the administration of *immature* dendritic cells." Thus, the production of tolerogenic dendritic cells genetically engineered using adenoviral vectors is unpredictable and is not a matter of routine screening. The instant invention is not enabled given the lack of guidance in the specification and the unpredictability in the art, relating to making an isolated tolerogenic dendritic cell and further comprising a viral vector. Applicant has not provided guidance for overcoming the contradictions needed to make an isolated tolerogenic dendritic cell that further comprises a viral vector, as discussed in the references discussed in Morelli et al., Rea et al., Zhong et al., and Tillman et al. Undue experimentation would be required to make the isolated tolerogenic dendritic cell that further comprises a viral vector and thus undue experimentation would be required to practice the invention throughout the full scope of the claims.

In the previous Office Action mailed August 26, 2004, Claims 15, and 17-29 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing tolerogenicity in a mammalian transplant host, comprising the intravenous administration of an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide, wherein the oligodeoxyribonucleotide is SEQ ID NO: 1, further comprising an adenoviral vector encoding CTLA4Ig, and further comprising incubating said isolated tolerogenic dendritic cell in the presence of GM-CSF, does not reasonably provide enablement for a method of enhancing tolerogenicity in a

mammalian host with an inflammatory related disease or arthritis, comprising any route of administration of an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, further comprising a viral vector, and further comprising incubating said isolated tolerogenic dendritic cell in the presence of one or more cytokines, TGF-β, FK 506, or cyclosporine A. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed August 26, 2004.

***Response to Arguments***

In response to the rejection, Applicants argue that the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. Applicants argue that the specification clearly enables a method for enhancing tolerogenicity in a mammalian host comprising propagating immature isolated dendritic cells from a mammalian donor, incubating the immature isolated dendritic cells with an oligodeoxyribonucleotide having at least one NF-κB binding site under conditions wherein the immature isolated dendritic cells internalize the oligodeoxribonucleotide, wherein the NF-κB binding sites inhibit NF-κB transcriptional activity, culturing the isolated dendritic cells of (b) to produce isolated tolerogenic dendritic cells, and administering said isolated tolerogenic dendritic cells to said host, wherein the oligodeoxribonucleotide has a sequence set forth in SEQ ID NO:1. Applicant relies on *In re Wands*.

Applicant's arguments have been fully considered, but are found persuasive. Applicants contend that the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. Applicants rely on *In re Wands*. However, the weighing of several factors as set forth in *Wands* was the standard applied under 35 USC 112, first

paragraph rejection in the previous Official Action mailed August 26, 2004. Because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

The instant claims are drawn to a method for enhancing tolerogenicity in a mammalian host comprising propagating immature isolated dendritic cells from a mammalian donor, incubating the immature isolated dendritic cells with an oligodeoxyribonucleotide having at least one NF-κB binding site under conditions wherein the immature isolated dendritic cells internalize the oligodeoxribonucleotide, wherein the NF-κB binding sites inhibit NF-κB transcriptional activity, culturing the isolated dendritic cells of (b) to produce isolated tolerogenic dendritic cells, and administering said isolated tolerogenic dendritic cells to said host, wherein the oligodeoxribonucleotide has a sequence set forth in SEQ ID NO:1. The specification as filed teaches methodologies for prolonging heart allograft survival in mice using bone marrow-derived dendritic cells pre-treated with SEQ ID NO: 1 (see Figure 8) and transfected with adenovirus encoding CTLA4Ig (see Table 1). The art teaches dendritic cells genetically engineered using adenoviral vectors are unpredictable. For example, see the discussions of Morelli et al., Rea et al. Zhong et al., and Tillman et al. above. Further, U.S. Patent No. 5,871,728 teaches a method for culturing *mature* dendritic cells comprising culturing dendritic cells in the presence of a cytokine and a extracellular matrix protein (see column 4, lines 15-19). Further, Giannoukakis et al. (Molecular Therapy, 2000 Vol. 1:430-437) teach, "*In vivo*, only the NF-κB-specific decoys were able to significantly prolong allogeneic heart survival, although some level of prolongation was observed in recipients infused with dendritic cells treated with one of the control oligonucleotides" (see page 436-437).

Giannoukakis et al. further teach, "Oligonucleotides can have sequence-nonspecific as well as aptameric effects" (see page 437). Even further, Flores-Romo (Immunology, 2001 Vol. 102:255-262) teaches, "despite the extensive research on dendritic cells recently, there remain significant gaps to be addressed, especially within the *in vivo* context" (see page 260, second column).

The instant specification at page 12 [00034] contemplates the viral vector comprising tolerogenic dendritic cell is useful for ameliorating inflammatory-related diseases, such as autoimmune diseases, including autoimmune arthritis, autoimmune diabetes, asthma, septic shock, lung fibrosis, glomerulonephritis, artherosclerosis, and AIDS. The instant specification teaches methodologies for prolonging heart allograft survival in mice using bone marrow-derived dendritic cells pre-treated with SEQ ID NO: 1 (see Figure 8) and transfected with adenovirus encoding CTLA4Ig (see Table 1). The specification does not demonstrate any correlation with prolonging heart allograft survival and ameliorating any inflammatory-related disease. The specification does not present any examples wherein treatment effects were obtained for any inflammatory-related diseases, including autoimmune arthritis, autoimmune diabetes, asthma, septic shock, lung fibrosis, glomerulonephritis, artherosclerosis, and AIDS using the viral vector comprising a tolerogenic dendritic cell of the instant claims.

The instant invention is not enabled given the lack of guidance in the specification and the unpredictability in the art relating to a method for enhancing tolerogenicity in a mammalian host comprising administering an isolated tolerogenic dendritic cell. Applicant has not provided guidance for overcoming the contradictions needed to make an isolated tolerogenic dendritic cell and further comprises a viral vector, as discussed in the references discussed in Morelli et al., Rea et al., Zhong et al., and Tillman et al. Further, the art teaches that cytokines, in the presence of

extracellular matrix proteins, induce *maturation* of dendritic cells, unlike the instant invention, which claims tolerogenic (immature) dendritic cells. Further, the art teaches that oligonucleotides can have sequence-nonspecific effects. Undue experimentation would be required to devise a method of enhancing tolerogenicity in a mammalian host comprising administering an isolated tolerogenic dendritic cell and thus undue experimentation would be required to practice the invention throughout the full scope of the claims.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-7, 9-15, 17-30, and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 7, 15, 17, and 30 recite the phrase, "wherein the NF-κB binding sites inhibit NF-κB transcriptional activity". This phrase doesn't makes sense because it is apparent that the *oligodeoxyribonucleotide* having one or more NF-κB binding sites *inhibits* NF-κB transcriptional activity, not the binding sites themselves.

Claims 9 and 17 are indefinite because they recite the phrase, "the presence of one or more cytokine" in line 2. This phrase is grammatically incorrect and should refer to one or more cytokine(s).

***Conclusion***

Claims 1, 2, 4-7, 9-15, 17-30, and 32-34 are free of the prior art. The closest prior art of record is that of Thomson et al. [U.S. Patent No. 5,871,728] who teach enhancing tolerogenicity in a mammal host comprising propagating immature dendritic cells from a mammalian donor, culturing the dendritic cells and administering the tolerogenic dendritic cells to the host. Thomson et al. do not teach or suggest an isolated tolerogenic dendritic cell comprising an oligodeoxyribonucleotide having one or more NF-κB binding sites, wherein the oligodeoxyribonucleotide inhibits NF-κB transcriptional activity, and wherein the oligodeoxyribonucleotide has the sequence set forth in SEQ ID NO:1.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
August 30, 2004

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600